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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/938,689 | 08/23/2001 | Manley Huang | 9342-028 | 3530 |

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GENENCOR INTERNATIONAL, INC.
ATTENTION: LEGAL DEPARTMENT
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| EXAMINER | |
|---|---|
| NGUYEN, QUANG | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/938,689 | HUANG ET AL. | |
| | Examiner | Art Unit | |
| | Quang Nguyen, Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17,19-22 and 24-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19-22 and 24-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4/22/03*.

4)☐ Interview Summary (PTO-413) Paper No(s). _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other:

## DETAILED ACTION

Applicants' amendment filed on 9/29/03 has been entered.

Amended claims 17, 19-22, 24-28 and new claims 29-39 are pending in the present application.

### *New Matter*

Amended claims 17, 19-21, 29-32 and new claims 34-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new ground of rejection necessitated by Applicants' amendment.**

Claim 17 and its dependent claims recite "further comprises a mutation in the I-Aβ gene". Claim 34 and it dependent claims recite "a human transgene comprising a nucleic acid sequence that encodes a MHC Class II molecule, wherein the transgene comprises naturally linked DRab and DQab alleles". There is literally no support in the originally filed specification for the make and use of a recipient mouse comprising any mutation in the I-Aβ gene or a recipient mouse comprising a human transgene comprising a nucleic acid sequence that encodes any MHC class II molecule (not necessarily limited to MHC Class II DR3 molecule), and wherein the transgene comprises naturally linked DRab and DQab alleles as claimed. Applicants fail to point out the specific page number and line number in the present specification that provide

support for such amendments. While the specification teaches the preparation of 4D1/C2D/RAG2 (HLA-transgenic) mice having a homozygous deletion of the MHC I-Aβ gene background and complete DRab and DQab alleles of DR3/DQ2 molecules, and (page 45, lines 7-8), there is no teachings or literal support for the make and use of any recipient mouse comprising any mutation in the I-Aβ gene or a recipient mouse comprising a human transgene comprising a nucleic acid sequence that encodes any MHC class II molecule, and wherein the transgene comprises naturally linked DRab and DQab alleles as claimed.

Therefore, given the lack of written support on this aforementioned issue from the originally filed specification, it would appear that Applicants did not have possession of the claimed invention at the time the application was filed.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 17, 19-21, 29-32 and new claims 34-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth immediately above. **This is a new ground of rejection necessitated by Applicants' amendment.**

As enablement requires the specification to teach how to make and use the claimed invention, with the lack of sufficient description and/or guidance provided by the instant specification at the time the application was filed regarding to the make and use of a recipient mouse comprising any mutation in the I-Aβ gene or a recipient mouse comprising a human transgene comprising a nucleic acid sequence that encodes any MHC class II molecule, and wherein the transgene comprises naturally linked DRab and DQab alleles as claimed, it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention.

**Additionally, the instant specification is also not enabled for the presently claimed invention for the reasons discussed in the Enablement rejection below.**

Amended claims 17, 19-22 and 24-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This is a new ground of rejection necessitated by Applicants' amendment.**

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

*Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Amended claims 17, 19-21 and new claims 29-33 are drawn to a recipient mouse comprising a disruption in both alleles of a gene, wherein said gene modulates VDJ recombination and furthermore such that lymphocyte maturation does not occur; and a human transgene comprising a nucleic acid molecule that encodes a MHC Class II DR3 molecule, wherein the transgene comprises naturally linked DRab and DQab alleles, wherein said transgene is incorporated into the genome of said recipient mouse; and further wherein said recipient mouse is immunodeficient and further comprises a mutation in the I-Aβ gene; the same with the various limitation recited in the dependent claims.

Amended claims 22, 24-28 are drawn to a method of making a recipient mouse, said method comprising: disrupting both alleles of a gene, wherein said gene modulates VDJ recombination and furthermore such that lymphocyte maturation does not occur; inserting a human transgene comprising nucleic acid that encodes MHC Class II DR3 and DQ2 molecules, wherein the DRab and DQab alleles are naturally linked, wherein said transgene is incorporated into the genome of said recipient mouse; and inactivating murine I-Eα and I-Aβ; and further wherein said recipient mouse is immunodeficient.

New claims 34-39 are drawn to a recipient mouse comprising: a disruption in both alleles of a gene, wherein said gene modulates VDJ recombination and furthermore such that lymphocyte maturation does not occur, and a human transgne comprising a nucleic acid sequence that encodes a MHC Class II molecule, wherein the

transgene comprises naturally linked DRab and DQab alleles, wherein said transgne is incorporated into the genome of said recipient mouse; and further wherein said recipient mouse is immunodeficient.

The specification teaches by exemplification showing the attainment of 4D1/C2D/RAG-2 mice (presumably via breeding between 4D1/CD2 double transgenic mice with RAG-2 mice) that express surface DR and not I-Eα, and wherein the mice appear to have a functional intact immune response (e.g., eliciting T-cell and antibody responses; see pages 42-46).

The above evidence has been noted and considered, however the instant specification is not enabled for the presently claimed invention for the reasons discussed below.

**(a)** ***The breadth of the claims***. The broad claims encompass the making of a recipient mouse whose genome comprises a disruption in both alleles of any gene as long as the gene modulates VDJ recombination and such that lymphocyte maturation does not occur, and said mouse contains a human transgene comprising a nucleic acid sequence encoding a MHC Class II DR3 molecule, wherein the transgene comprises naturally linked DRab and DQab alleles, and wherein said transgene is incorporated into the genome of said recipient mouse, and said recipient mouse further comprises any mutation in the I-Aβ gene and said recipient mouse is immunodeficient; and any methods of making the same recipient mouse using any material for disrupting both alleles of a gene involved in lymphocyte maturation, for inserting a transgene comprising nucleic acid sequence encoding a MHC Class II DR3 molecule, wherein the

DRab and DQab alleles are naturally linked and for inactivating murine I-Eα and I-Aβ. The method claims also encompass the concurrent introduction of nucleic acid sequences for disrupting both alleles of a gene that modulates VDJ recombination, for inserting a transgene comprising nucleic acid sequence encoding a MHC Class II DR3 molecule, wherein the DRab and DQab alleles are naturally linked and for inactivating murine I-Eα and I-Aβ into any cell for the generation of the recipient mouse. New claim 34 and its dependent claims encompass an immunodeficient recipient mouse comprising any nucleic acid sequence that encodes any MHC Class II molecule (not necessarily limited to a MHC Class II DR3 molecule) with naturally linked DRab and DQab alleles.

***(b) The state and the unpredictability of the prior art***. At the filing date of the present application, the art of transgenesis was known to be highly unpredictable with respect to the unpredictability of the incorporation and expression of the transgenes as well as the knockout of any genes to attain any desired phenotype in any animal species as a result of such modification(s). It should be noted that the level and specificity of the specific transgene (for this instance a human transgene encoding a MHC Class II DR3 molecule, wherein the transgene comprising naturally linked DRab and DQab alleles) as well as the resulting phenotype of the transgenic mouse are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome are all important factors in controlling the expression of a transgene in the production of transgenic

animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology 45:57-68, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (page 61, last paragraph). Moreadith et al. (J. Mol. Med. 75:208-216, 1997) supports phenotypic unpredictability in knockout mice. In particular, Moreadith et al. discuss that gene targeting at a particular locus is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many instances, changes the prevailing notions regarding the functions of the encoded proteins. For example, Moreadith et al. report that gene targeting at the endothelial loci led to the creation of mice with Hirschsprung's disease instead of the anticipated phenotype of abnormal control of blood pressure (See page 208, column 2, second paragraph). The unpredictability of the resulting phenotypes for HLA transgenic mice is also supported by recent results of Chen et al. (J. Immunol. 168:3050-3056, 2002) and Chen et al. (Eur. J. Immunol. 33:172-182, 2003). Using a large 550kb YAC construct encompassing both HLA-DR3/DQ2, the HLA DR3/DQ2 transgenic mice in an I-Aβ° background of Chen et al. (Eur. J. Immunol.) show DR expression in resting or activated T lineage cells whereas the HLA DR3-DQ2 transgenic mice in the same background generated from a shorter 320kb construct by Chen et al. (J. Immunol.) do not.

***(c) The amount of direction or guidance provided***. In light of the state of the prior art at the filing date of the present application, the instant specification is not enabled for the presently broadly claimed invention. This is because apart from the exemplification showing the attainment of 4D1/C2D/RAG-2 mice in the I-Aβ°

background (presumably via breeding between 4D1/CD2 double transgenic mice with RAG-2 mice) that express surface DR and not I-Eα, and wherein the mice appear to **have a functional intact immune response** (e.g., eliciting T-cell and antibody responses to fungal proteases, hybrid protein, HSP65 epitope, tetanus toxoid and KLH; see pages 42-46), the instant specification does not provide sufficient guidance for a skilled artisan on how to obtain any recipient mouse with the immunodeficient phenotype as claimed. As defined by the present application, the term "immunodeficiency" refers to a lack of antigen-specific immunity in a mammal (see page 5, lines 15-16), and the phenotype disclosed for 4D1/C2D/RAG-2 mice is not consistent with the phenotype being claimed for a recipient mouse, let alone for any recipient mouse comprising a disruption in both alleles of any gene as long as it modulates VDJ recombination and any nucleic acid sequence that encodes any MHC Class II molecule. In the absence of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention.

The instant specification also does not provide sufficient guidance for a skilled artisan on how to obtain the recipient mouse as claimed using any methods with any materials as long as both alleles of a gene that modulates VDJ recombination are disrupted, the murine I-Eα and I-Aβ are inactivated and the human transgene encoding any MHC Class II molecule (including MHC class II DR3 molecule), wherein the transgene contains naturally linked DRab and DQab alleles is inserted. It is noted that apart from the teachings of introducing the human HLA transgene into an ES cell, and

making the transgenic recipient mouse through breeding with known RAG2 and I-Eα deficient mouse strains, the instant specification fails to provide sufficient guidance for a skilled artisan on how to obtain the claimed recipient mouse by any method (e.g., concurrent introduction of all knockout gene constructs and a human MHC Class II transgene into an embryonic stem cell, spontaneous mutation, irradiation as well as using an antisense approach to inactivate or disrupt any gene). Therefore, in the absence of sufficient guidance provided by the instant disclosure, it would also have required undue experimentation for a skilled artisan to make and use the full breadth of the presently claimed invention. The physiological art is recognized as unpredictable (MPEP 2164.03). Particularly, it is already noted by Applicants that unlike RAG-1 and TCRβ/δ_mutant mice, $RAG2^{-/-}$ mouse strain confers a unique support for the functional development of allogeneic HSC without any radiation, and that SCID mice are not able to support functional development of allogeneic HSC (see Table 2).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the transgenic and physiological arts in general, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the presently claimed invention.

***Response to Applicants' argument***

Applicants' arguments related to certain issues in the above rejection in the Amendment filed on 9/29/03 (pages 16-17) have been fully considered, but they are not found persuasive.

With respect to the unpredictability of the art, Applicants argue that at the time the specification was filed, the expression of human HLA Class II transgenes in transgenic animals derived from the use of large fragments of human genomic DNA provides a sufficient amount of regulatory information for the long-term and functional expression of MHC Class II molecule in transgenic mice as evidenced by the teachings of Gonzalez-Gay; Straub et al., Nishimura et al., Wen et al. Additionally, RAG-1 gene, RAG-2 gene, T cell receptor gene and immunoglobulin genes were known as well as the effects of I-E$\alpha$ and I-A$\beta$ were well known. Therefore, the present application as filed provides in-depth descriptions of how transgenic animals can be produced, screened for various phenotypic characteristics and utilized.

The examiner notes that the unpredictability of the art is only one of the Wand factors to be evaluated for the enablement of the presently claimed invention. Furthermore, none of the references cited by Applicants teaches a transgenic recipient mouse with all the limitations recited by the instant claims and by any method as contemplated by Applicants. Additionally, the instant specification fails to teach a representative number of species of claimed transgenic recipient mice having a disruption of both alleles of a gene which **modulates** VDJ recombination such that lymphocyte maturation does not occur. Which of the RAG-1 gene, RAG-2 gene, T cell

receptor gene and which immunoglobulin genes **upregulates or down-regulates** (within the scope of the term "modulate") VDJ recombination? With the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention.

***Written Description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 17, 20-22, 34, 36 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons already set forth in the previous Office Action mailed March 27, 2003 (pages 2-5).

***Response to Applicants' argument***

Applicants' arguments related to the above rejection in the Amendment filed on 9/29/03 (pages 15-16) have been fully considered, but they are not found persuasive.

Applicants argue mainly that the amendment reciting the disruption in both alleles of a gene involves a gene which **modulates** VDJ recombination such that lymphocyte maturation does not occur should overcome the Written Description. Applicants' argument is not persuasive because the instant specification still fails to teach a

representative number of species of claimed transgenic recipient mice having a disruption of both alleles of a gene which **modulates** VDJ recombination such that lymphocyte maturation does not occur. This is because as the term "modulates" encompass both up-regulating as well as down-regulating VDJ recombination, the instant specification fails to teach a representative number of genes that upregulate as well as down-regulate VDJ recombination to be disrupted for the making and using a transgenic mouse as claimed. On the basis of the present disclosure, it is unclear which of the disclosed genes RAG-1, RAG-2, TCR, Ig genes, SCID and others including genes that have not been isolated or characterized can up-regulate or down-regulate VDJ recombination. Therefore, the skilled artisan can not envision the detailed structure of a transgenic recipient mouse as broadly claimed and the broadly claimed method for making the same, and therefore conception is not achieved until reduction to practice has occurred.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 24-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new ground of rejection necessitated by Applicants amendment.**

Claims 22 and 24-28 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential essential components and/or essential steps. As

written, it is unclear how both alleles of a gene involved in lymphocyte maturation (e.g., RAG-2 gene) are disrupted and in which cells the disruption is carried out; and how a transgene comprising a nucleic acid that encodes MHC Class II DR3 and DQ2 molecules, wherein the DRab and DQab alleles are naturally linked is inserted and in which cells; and how murine I-Eα and I-Aβ are inactivated in which cells, and how are these active steps (e.g., disrupting, inserting and inactivating) are connected to a recipient mouse as claimed. The metes and bounds of the claims are not clearly determined.

Additionally, in claim 22 it is unclear what is encompassed by the phrase "encodes MHC Class II DR3 and DR3 molecule". The metes and bounds of the claims are not clearly determined.

***Response to Applicants' argument***

Applicants' arguments related to certain issues in the above rejection in the Amendment filed on 9/29/03 (page 18) have been fully considered, but they are not found persuasive.

Applicants argue mainly that it is not intended that the present claims be limited to any specific means for gene disruption, introduction of transgenes, and/or inactivation of I-Eα is accomplished, as those of skill in the art will appreciate that various methods find use with the present invention. Applicants further argue with based on the present specification and the knowledge of those of skill in the art, the claims are definite.

Applicants' arguments are not found persuasive because the claims are not clear as written for the reasons already set forth above, and that the claims should not have to rely on the detailed description of the specification for to know the metes and bounds of the claims.

***Conclusions***

***No claims are allowed.***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

JAMES KETTER
PRIMARY EXAMINER